BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 7 1953

ISONIAZID IN COMBINATION WITH STREPTOMYCIN OR WITH P.A.S. IN THE TREATMENT OF PULMONARY TUBERCULOSIS

FIFTH REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS CHEMOTHERAPY TRIALS COMMITTEE*

The Medical Research Council trial of isonicotinic acid hydrazide (isoniazid) in the treatment of pulmonary tuberculosis has been in progress since March, 1952; reports comparing clinical and bacteriological findings in patients treated with streptomycin plus P.A.S., isoniazid alone, and streptomycin plus isoniazid, and a report on bacteriological techniques, have already been published (Medical Research Council, 1952, 1953a, 1953b, 1953c). The present report compares the effects of two combinations of drugs—streptomycin plus isoniazid and P.A.S. plus isoniazid—on a total of 391 patients after three months' treatment in 50 hospitals. A list of the hospitals, and the names of the co-operating clinicians, bacteriologists, and pathologists, are given at the end of the report. The trial was co-ordinated by the late Dr. Marc Daniels and by Dr. Wallace Fox, of the Council's Tuberculosis Research Unit; Dr. Fox and Dr. Ian Sutherland (of the Council's Statistical Research Unit) analysed the present results and prepared the report. Radiological assessments were made by Dr. L. G. Blair. The isoniazid used throughout the trial has been supplied as "nydrazid" by E. R. Squibb and Sons.

I. PLAN AND CONDUCT OF THE TRIAL

The plan and conduct of the trial are only briefly referred to here, as they have been described in detail in the first two reports (Medical Research Council, 1952, 1953a).

1. Type of Case

Certain basic requirements were laid down for all cases accepted into the trial. At the start of treatment: (*a*) Tubercle bacilli must have been demonstrated, either in a direct smear from a sputum specimen taken within the previous two weeks or in a culture derived from a specimen taken not more than two months previously. (*b*) The tubercle bacilli must not, so far as is known, be streptomycin-resistant or P.A.S.-resistant. (*c*) The patient must not have had more than 15 g. streptomycin or 300 g. P.A.S. (sodium salt) within the previous three months, and not more than 3 g. isoniazid at any time. (*d*) The patient must not be undergoing pneumoperitoneum, nor have any form of collapse therapy for the lung requiring treatment.

Cases satisfying the above requirements were admitted to the trial in one of three main disease groups: (1) acute rapidly progressive pulmonary tuberculosis believed to be of recent origin; (2) other forms of pulmonary tuberculosis considered suitable for chemotherapy; (3) chronic forms of pulmonary tuberculosis expected to make only a limited response to streptomycin plus P.A.S.

Group 1 cases were selected by a central panel of clinicians; cases in Groups 2 and 3 were, in the main, selected by the clinicians in the co-operating hospitals from the patients already under their care.

2. Treatment

When a patient has been accepted for the trial, treatment is allocated by the Tuberculosis Research Unit from confidentially held prearranged lists based upon random sampling numbers.

After admission to the trial and a preliminary week of investigation, all patients are kept under observation for six months. During the first three months the prescribed treatment is followed for every patient. During the second three months Group 3 patients continue on the same combination of drugs. For other patients the clinician is free to undertake any treatment he wishes.

In the present phase of the trial, which started on September 5, 1952, four treatments are being studied—namely:

SH: Streptomycin 1 g. daily, in one intramuscular injection, plus isoniazid 200 mg. daily, in two equal doses by mouth.

S2H: Streptomycin 1 g., in one intramuscular injection, twice a week, plus isoniazid 200 mg. daily, in two equal doses by mouth.

20 PH: P.A.S. (sodium salt) 20 g. daily, in four equal doses by mouth, plus isoniazid 200 mg. daily, in two equal doses by mouth.

10 PH: P.A.S. (sodium salt) 10 g. daily, in two equal doses by mouth, plus isoniazid 200 mg. daily, in two equal doses by mouth.

In one important disease subgroup (1A—acute rapidly progressive bilateral pulmonary tuberculosis of recent origin, in patients between the ages of 15 and 30) patients have been allocated only to the SH and 20 PH series. Every other patient has been allocated at random to one of the four treatment series.

The present report analyses the results after three months' treatment for 391 patients admitted to the trial

*Members of the Committee: Sir Geoffrey Marshall (chairman), Professor J. W. Crofton, Professor R. Cruickshank, Dr. J. E. Geddes, Professor F. R. G. Heaf, Professor A. Bradford Hill, Dr. J. V. Hurford, Dr. D. A. Mitchison, Dr. W. D. M. Paton, Dr. J. G. Scadding, Dr. Norman Smith, Dr. P. D'Arcy Hart (secretary).

between September 5, 1952, and March 31, 1953. Over 200 more patients were admitted to the same four treatments between April 1 and July 31, 1953, when admissions to the trial were discontinued; the three-month results for these latter patients are not yet complete. It should also be noted that the results for the 142 SH patients previously reported (Medical Research Council, 1953a) do not appear in the present analysis because they formed part of an earlier comparison.

3. Number of Patients in the Present Analysis

Prior to exclusions, 125 patients were allocated to the SH treatment, 104 to S2H, 121 to 20 PH, and 82 to 10 PH. The larger totals in the SH and 20 PH series are accounted for by patients in subgroup 1A. The number of patients allocated to the S2H series is not intentionally larger than the number in the 10 PH series; the difference has arisen by chance as a result of the operation of random allocation in the 50 hospitals.

Forty-one patients were excluded from the analysis of the results for the following reasons :

(i) Five patients were excluded before treatment was started:
- 1 died before admission to hospital (20 PH);
- 1 was too ill to be moved to hospital (S2H);
- 2 discharged themselves against medical advice (2 20 PH);
- 1, although admitted, did not start treatment, because no positive sputum was obtained (SH).

(ii) Thirty-six patients were excluded after treatment had begun:
- 2 were found to have had organisms resistant to streptomycin at the start of treatment (2 SH);
- 4 were found to have had organisms resistant to P.A.S. at the start of treatment (3 20 PH, 1 10 PH);
- 6 were found to have had excessive recent chemotherapy (1 S2H, 4 20 PH, 1 10 PH);
- 1 was given the wrong treatment (20 PH);
- 11 discharged themselves against medical advice—6 in the first and 5 in the second month (1 SH, 2 S2H, 2 20 PH, 6 10 PH);
- 2 were transferred to other hospitals in the first month for investigations of non-pulmonary complaints (1 20 PH, 1 10 PH);
- 1 was transferred to a mental hospital with a psychosis, in the second month (10 PH);
- 3 had severe toxic reactions attributed to P.A.S. (3 20 PH);
- 2 stopped treatment in the second month, one because of acute nephritis, the other because of persistent haemoptysis believed to be related to treatment (2 SH);
- 2 had a change of treatment in the first month: for one 10 PH patient streptomycin was added after eight days, and the dosage of P.A.S. was doubled, because of the serious clinical condition; this case can scarcely be considered a failure of the prescribed chemotherapy: in one 20 PH patient streptomycin was added after 18 days because of radiographic deterioration; this patient had 1-minus deterioration at one month, and the deterioration at three months was still classed as 1-minus; despite the short period of treatment, this may represent a failure of the prescribed chemotherapy;
- 2 had a change of treatment in the second month (2 20 PH): one patient had deteriorated both clinically and radiographically and the treatment was changed to SH at six weeks; at ten weeks a radiograph showed 1-plus improvement compared with the condition on admission: the other patient deteriorated radiographically and streptomycin was added at six weeks, but there was 2-minus deterioration at three months.

Thus in the present series only 3 patients were removed from the trial because of drug toxicity; all were receiving 20 PH and were intolerant to the P.A.S. In 2 more (2 SH) drug toxicity could not be excluded as the cause of acute nephritis in one and persistent haemoptysis in the other, although in the latter patient the same chemotherapy was resumed after an interruption of five weeks without a recurrence of the haemoptysis.

Of the 4 patients in whom treatment was changed, 2, and possibly a third, all on 20 PH, might be classed as failures of treatment. On the other hand, it must be remembered that the combination P.A.S. plus isoniazid was a new treatment; it would be a natural inclination for clinicians to resort to a combination containing streptomycin for patients who deteriorated.

4. Plan of the Present Report

After the exclusions detailed above, the numbers remaining in the clinical analysis are 119 SH, 100 S2H, 101 20 PH, and 71 10 PH patients. The numbers in each disease group are set out in Table I. It should be noted, first, that in contrast to the earlier reports on the trial the total of very chronic patients (Group 3) is small and that the proportion of patients admitted to the trial who were suffering from acute forms of the disease has been higher in recent months than in earlier stages. Secondly, since patients in subgroup 1A (acute bilateral disease in young adults) were admitted only to the SH and 20 PH treatment series, a valid comparison of the relative clinical efficacy of all four treatments SH, S2H, 20 PH, and 10 PH can be made only after excluding the patients in subgroup 1A. When this is done, the clinical results of the four treatments are at present very similar, although the numbers of patients are too small for firm conclusions to be reached. A full comparison of the four treatments will be made when results on a larger number of patients are available.

In this report two comparisons are made. First, the clinical progress of patients on the SH and 20 PH treatments is compared, and for this purpose the 70 patients in sub-

TABLE I.—*Number of Patients Admitted to the SH, S2H, 20 PH, and 10 PH Treatments from September 5, 1952, to March 31, 1953 (after exclusions)*

	Treatment				All Patients
	SH	S2H	20 PH	10 PH	
	Streptomycin 1 g. Daily Plus Isoniazid 200 mg. Daily	Streptomycin 1 g. Twice a Week Plus Isoniazid 200 mg. Daily	P.A.S. (Sodium) 20 g. Daily Plus Isoniazid 200 mg. Daily	P.A.S. (Sodium) 10 g. Daily Plus Isoniazid 200 mg. Daily	
Group 1: Acute rapid y progressive pulmonary tuberculosis of recent origin — 1A. Bilateral; ages 15–30	39	—	31	—	70
1B. Bilateral; other ages / 1C. Unilateral; all ages	25	25	17	23	90
Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	52	67	45	44	208
Group 3: Chronic forms of pulmonary tuberculosis expected to make only a limited response to chemotherapy	3	8	8	4	23
All patients	119	100	101	71	391

group 1A are included, but the 11 Group 3 patients are omitted because of their small number and unequal distribution between the two treatments; this leaves 116 SH patients and 93 20 PH patients. The results are presented in Section A of Tables II–VII. Secondly, a supplementary comparison of streptomycin plus isoniazid and P.A.S. plus isoniazid on a large number of patients is made by combining all the SH and S2H patients, numbering 219, and comparing their progress with that of all the 20 PH and 10 PH patients, numbering 172. Group 3 patients have been retained in this broad comparison, the results of which appear in Section B of Tables II–VII.

II. CLINICAL PROGRESS

1. Condition on Admission

The treatment which patients had received before entering the trial was analysed. Eight patients on SH (7%), 8 on S2H (8%), 6 on 20 PH (6%), and 3 on 10 PH (4%) had already received one or more courses of chemotherapy, but not within the preceding three months. For the patients in Groups 1 and 2 combined, the figures for the four treatments are 7 (6%), 4 (4%), 2 (2%), and 2 (3%), respectively. Thus most of the patients in the present analysis were receiving their first course of chemotherapy in this trial. Most were also newly diagnosed cases.

Table II shows the condition of patients before the start of treatment as reflected by their general condition (assessment by the clinician in charge), temperature, erythrocyte sedimentation rate (E.S.R. Westergren 200 mm. reading at one hour), and the extent of cavitation on a full-plate radiograph (as estimated by an independent radiological assessor, unaware of the treatment series of any patient). It can be seen that, judging by the factors listed, the SH and 20 PH patients (Section A of the Table) had a broadly similar distribution of severe and less severe illness, but that, particularly in Group 2, the SH patients appear to have been, on the average, rather less ill than the 20 PH patients. This possible disadvantage to the 20 PH treatment must be borne in mind in assessing the results. The patients in the SH and S2H series combined (Section B of the Table) had a distribution of severe and less severe illness similar to that of the 20 PH and 10 PH patients.

2. Mortality

There were two deaths among the 391 patients (0.5%) during the three months of treatment—one in an SH patient, the other in a 20 PH patient. The SH patient (in Group 1) died towards the end of the third month with renal failure secondary to acute nephritis, confirmed at post-mortem examination. This patient had slight clinical and radiographic deterioration at one month and showed further clinical and radiographic deterioration at the end of two months. The nephritis was diagnosed in the third month. The 20 PH patient (in subgroup 1A) rapidly deteriorated, and treatment was stopped after 20 days because the patient was incapable of swallowing; she died 10 days later.

3. Toxicity

Apart from the 3 exclusions due to P.A.S. toxicity, and the 2 doubtful toxic reactions described above, there is nothing new to report on toxicity. With the dosage used (200 mg. daily), there continues to be no evidence of serious toxicity from isoniazid therapy over a three-month period of administration. In one 20 PH patient treatment was stopped after 10 weeks because the leucocyte count fell progressively from 4,400 per c.mm. to 1,800 per c.mm., although the differential count remained normal. It was considered undesirable to continue chemotherapy, but the patient has been retained in the analysis at three months.

4. The Comparison between SH (Streptomycin 1 g. Daily Plus Isoniazid 200 mg. Daily) and 20 PH (P.A.S., Sodium Salt, 20 g. Daily Plus Isoniazid 200 mg. Daily)

General Condition.—Change in the patient's general condition was assessed by the physician in charge. Section A of Table III shows that a high percentage of patients on each treatment improved—89% of 116 SH patients and 88% of 93 20 PH patients. With each treatment there were more patients with 2-plus (considerable) improvement in Group 1 than in Group 2.

Weight Changes.—The weight changes for the three-month period are set out in Section A of Table IV. Only 6 of 113 SH patients (5%) and 9 of 90 20 PH patients (10%) failed to gain weight. A gain of 14 lb. (6.4 kg.) or more occurred in 45% of SH patients and 38% of 20 PH patients, and

TABLE II.—*Condition on Admission of Patients Treated with Isoniazid in Combination with Streptomycin or with P.A.S.*

		Treatment	Total	General Condition			Average Evening Temperature in Pre-treatment Week*				Erythrocyte Sedimentation Rate (Westergren 200 mm. Reading at 1 Hour)				Extent of Cavitation†			
				Good	Fair	Poor	Afebrile	Under 99° F.	99–99·9° F	100° F. or more	0–10	11–20	21–50	51 or more	Nil	1-plus	2-plus	3-plus
			No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Section A	Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SH	64 100	14 22	26 41	24 38	20 31	18 28	16 25	10 16	5 8	6 9	25 39	28 44	9 14	13 20	30 47	12 19
		20 PH	48 100	8 17	19 40	21 44	11 23	20 42	10 21	7 15	2 4	3 6	21 44	22 46	5 10	15 31	21 44	7 15
	Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SH	52 100	24 46	19 37	9 17	34 65	11 21	5 10	2 4	16 31	10 19	18 35	8 15	15 29	20 38	16 31	1 2
		20 PH	45 100	12 27	17 38	16 36	20 44	15 33	6 13	4 9	10 22	10 22	17 38	8 18	13 29	13 29	14 31	5 11
	Groups 1 and 2 combined	SH	116 100	38 33	45 39	33 28	54 47	29 25	21 18	12 10	21 18	16 14	43 37	36 31	24 21	33 28	46 40	13 11
		20 PH	93 100	20 22	36 39	37 40	31 33	35 38	16 17	11 12	12 13	13 14	38 41	30 32	18 19	28 30	35 38	12 13
Section B	All patients in Groups 1, 2, and 3 combined	SH and S2H	219 100	74 34	85 39	60 27	99 45	66 30	31 14	23 11	39 18	33 15	81 37	66 30	44 20	66 30	81 37	28 13
		20 PH and 10 PH	172‡ 100	46 27	69 40	57 33	67 39	57 33	30 17	18 10	27 16	24 14	70 41	50 29	44 26	49 28	62 36	17 10

* A patient was considered afebrile if *every* evening temperature in the pre-treatment week of investigation was below 99° F. (37·2° C.).
† Assessment on a single full-plate chest radiograph taken before treatment started. Tomograms were not taken into account.
‡ The sedimentation rate of one patient was not recorded.

the average weight gain for the former was 12.8 lb. (5.8 kg.), for the latter 10.8 lb. (4.9 kg.). These differences for Groups 1 and 2 combined do not attain statistical significance. However, in Group 1 alone, the difference in average weight gain is significant at the 1% level.

Temperature.—A patient was considered to be initially afebrile if the evening temperature was below 99° F. (37.2° C) on *every day* of the week of preliminary investigation. The same definition applied in the last week of the third month of treatment. Table V sets out the number of patients who were febrile in the pre-treatment week but afebrile at three months. The patients are grouped according to the initial level of pyrexia. Of 61 febrile SH patients, 79% were afebrile at three months, compared with 85% of the same number of febrile 20 PH patients. Of 54 SH patients who were afebrile in the pre-treatment week (not shown in the Table), 8, or 15%, had a low-grade pyrexia at three months (an occasional evening temperature above 99° F.). The corresponding figures for the 20 PH patients were 4 of 31, or 13%.

Sedimentation Rate.—Table VI sets out the number of patients with an initially elevated E.S.R. which was lowered to normal (10 or less) after three months' treatment. The E.S.R. was normal at the end of three months in 37% of 78 SH patients with an initial E.S.R. of 21 or more. The corresponding figures for the 20 PH series were 46% of 67 patients. The difference is not statistically significant. The E.S.R. rose from an initially normal level in 2 of 21 SH patients and 2 of 12 20 PH patients.

Radiographic Changes in the First Three Months.—Table VII sets out the radiographic changes at the end of three months' treatment. The assessments were made at an independent reading of full-plate chest radiographs by a radiologist unaware of the treatment of any patient. In assessing improvement or deterioration three degrees were allowed in each—namely, 1-plus, 2-plus, and 3-plus, and 1-minus, 2-minus, and 3-minus. Of 116 SH patients 82% improved radiographically, compared with 76% of 93 20 PH patients. Two-plus and 3-plus improvement was more frequent under the SH treatment (54%) than the 20 PH treatment (42%). In Group 1, 23% of 64 SH patients showed 3-plus (considerable) improvement compared with 10% of 48 20 PH patients. These differences do not attain statistical significance. In all, there were two radiographic deteriorations and one death on each treatment.

Summary of the Comparison of SH with 20 PH

At the end of three months the two treatments had very similar effects on the general condition of the patient and on the temperature. The 20 PH treatment may have been slightly the more effective in lowering the E.S.R., and the SH treatment in fostering weight gain. Judging from the important assessment of radiographic response, the SH treatment appears to have been rather more effective, particularly in the cases with acute extensive disease in Group 1. The 20 PH patients were on an average more ill than the SH patients on admission to the trial (Table II), and so may have started at a disadvantage. On the other hand, it will be recalled that 3 20 PH patients, who deteriorated and had their treatment changed, were excluded from the analysis.

TABLE III.—*General Condition at the End of the Third Month Compared with General Condition on Admission*

		Treatment	Total	Improvement		No Change	Deterioration		Death
				2-plus	1-plus		1-minus	2-minus	
			No. %	No. %	No. %	No. %	No. %	No. %	No. %
Section A	Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SH	64 *101*	27 *42*	33 *52*	3 *5*	0 *0*	0 *0*	1 *2*
		20 PH	48 *100*	22 *46*	21 *44*	4 *8*	0 *0*	0 *0*	1 *2*
	Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SH	52 *100*	13 *25*	30 *58*	9 *17*	0 *0*	0 *0*	0 *0*
		20 PH	45 *100*	13 *29*	26 *58*	6 *13*	0 *0*	0 *0*	0 *0*
	Groups 1 and 2 combined	SH	116 *99*	40 *34*	63 *54*	12 *10*	0 *0*	0 *0*	1 *1*
		20 PH	93 *101*	35 *38*	47 *51*	10 *11*	0 *0*	0 *0*	1 *1*
Section B	All patients in Groups 1, 2, and 3 combined	SH and S2H	219 *99*	71 *32*	123 *56*	23 *11*	1 *0*	0 *0*	1 *0*
		20 PH and 10 PH	172 *100*	59 *34*	93 *54*	19 *11*	0 *0*	0 *0*	1 *1*

TABLE IV.—*Weight Changes in the First Three Months*

		Treatment	Total Weighed	Weight Gain				No Change	Weight Loss		Average Gain in Weight per Patient (lb.)
				21 lb. or More	14–20 lb.	7–13 lb.	Less than 7 lb.		Less than 7 lb.	7 lb. or More	
			No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	
Section A	Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SH	62 *101*	14 *23*	20 *32*	18 *29*	8 *13*	0 *0*	1 *2*	1 *2*	14·4
		20 PH	47 *99*	6 *13*	11 *23*	14 *30*	11 *23*	2 *4*	3 *6*	0 *0*	10·2
	Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SH	51 *100*	7 *14*	10 *20*	17 *33*	13 *25*	2 *4*	1 *2*	1 *2*	10·8
		20 PH	43 *100*	5 *12*	12 *28*	12 *28*	10 *23*	0 *0*	4 *9*	0 *0*	11·4
	Groups 1 and 2 combined	SH	113 *102*	21 *19*	30 *27*	35 *31*	21 *19*	2 *2*	2 *2*	2 *2*	12·8
		20 PH	90 *100*	11 *12*	23 *26*	26 *29*	21 *23*	2 *2*	7 *8*	0 *0*	10·8
Section B	All patients in Groups 1, 2, and 3 combined	SH and S2H	214 *99*	40 *19*	66 *31*	65 *30*	33 *15*	3 *1*	5 *2*	2 *1*	13·4
		20 PH and 10 PH	168 *100*	25 *15*	41 *24*	50 *30*	37 *22*	4 *2*	10 *6*	1 *1*	11·6

For two other patients on SH, two on S2H, two on 20 PH, and one on 10 PH the weight changes are not available. Also one SH patient and one 20 PH patient had died. (7 lb. = 3·2 kg. 14 lb. = 6·4 kg. 21 lb. = 9·5 kg.)

TABLE V.—*Number of Cases Febrile in the Pre-treatment Week who were Afebrile at the End of the Third Month*

		Treatment	Average Evening Temperature in the Pre-treatment Week						All Patients Febrile in the Pre-treatment Week	
			Under 99° F.		99° F.–99·9° F.		100° F. or More			
			Total	No. Afebrile at Three Months	Total	No. Afebrile at Three Months	Total	No. Afebrile at Three Months	Total	Afebrile at Three Months
										No. %
Section A	Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SH	18	15	16	14	9	6	43	35 *81*
		20 PH	20	19	10	9	6	4	36	32 *89*
	Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SH	11	10	5	2	2	1	18	13 *72*
		20 PH	15	14	6	4	4	2	25	20 *80*
				No. %		No. %		No. %		
	Groups 1 and 2 combined	SH	29	25 *86*	21	16 *76*	11	7 *64*	61	48 *79*
		20 PH	35	33 *94*	16	13 *81*	10	6 *60*	61	52 *85*
Section B	All patients in Groups 1, 2, and 3 combined	SH and S2H	66	56 *85*	31	21 *68*	22	12 *55*	119	89 *75*
		20 PH and 10 PH	57	48 *84*	30	25 *83*	17	10 *59*	104	83 *80*

One SH and one 20 PH patient, who died, are excluded from this table.

TABLE VI.—*Number of Cases with a Raised Erythrocyte Sedimentation Rate in the Pre-treatment Week Whose Sedimentation Rate was Normal at the End of the Third Month*

		Treatment	Sedimentation Rate in the Pre-treatment Week						All Cases with Initial Sedimentation Rate of 21 or More	
			11–20		21–50		51 or More			
			Total	No. with E.S.R. 0–10 at 3 Months	Total	No. with E.S.R. 0–10 at 3 Months	Total	No. with E.S.R. 0–10 at 3 Months	Total	E.S.R. of 0-10 at 3 Months
										No. %
Section A	Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SH	6	4	24	13	28	4	52	17 *33*
		20 PH	3	3	20	14	22	7	42	21 *50*
	Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SH	10	9	18	11	8	1	26	12 *46*
		20 PH	10	8	17	10	8	0	25	10 *40*
				No. %		No. %		No. %		
	Groups 1 and 2 combined	SH	16	13 *81*	42	24 *57*	36	5 *14*	78	29 *37*
		20 PH	13	11 *85*	37	24 *65*	30	7 *23*	67	31 *46*
Section B	All patients in Groups 1, 2, and 3 combined	SH and S2H	33	27 *82*	79	43 *54*	66	12 *18*	145	55 *38*
		20 PH and 10 PH	24	19 *79*	69	38 *55*	50	13 *26*	119	51 *43*

For one other SH patient the sedimentation rate at three months is not available. Also one SH and one 20 PH patient had died.

TABLE VII.—*Changes in Radiographic Appearances in the First Three Months*

		Treatment	Total	Improvement			No Change	Deterioration			Death
				3-plus	2-plus	1-plus*		1-minus	2-minus	3-minus	
			No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %	No. %
Section A	Group 1: Acute rapidly progressive pulmonary tuberculosis of recent origin	SH	64 *101*	15 *23*	22 *34*	19 *30*	5 *8*	1 *2*	1 *2*	0 *0*	1 *2*
		20 PH	48 *99*	5 *10*	16 *33*	16 *33*	9 *19*	1 *2*	0 *0*	0 *0*	1 *2*
	Group 2: Other forms of pulmonary tuberculosis suitable for chemotherapy	SH	52 *100*	12 *23*	14 *27*	13 *25*	13 *25*	0 *0*	0 *0*	0 *0*	0 *0*
		20 PH	45 *100*	9 *20*	9 *20*	16 *36*	10 *22*	1 *2*	0 *0*	0 *0*	0 *0*
	Groups 1 and 2 combined	SH	116 *101*	27 *23*	36 *31*	32 *28*	18 *16*	1 *1*	1 *1*	0 *0*	1 *1*
		20 PH	93 *99*	14 *15*	25 *27*	32 *34*	19 *20*	2 *2*	0 *0*	0 *0*	1 *1*
Section B	All patients in Groups 1, 2, and 3 combined	SH and S2H	219 *99*	40 *18*	68 *31*	61 *28*	42 *19*	2 *1*	5 *2*	0 *0*	1 *0*
		20 PH and 10 PH	172 *101*	25 *15*	41 *24*	61 *35*	38 *22*	5 *3*	1 *1*	0 *0*	1 *1*

* The assessments for one SH and one 10 PH patient were made by the clinician in charge. The *x*-ray films were subsequently lost.

5. The Comparison between Streptomycin Plus Isoniazid (SH and S2H) and P.A.S. Plus Isoniazid (20 PH and 10 PH)

General Condition.—Section B of Table III shows that the majority of patients—89% of 219 SH and S2H patients, and 88% of 172 20 PH and 10 PH patients—improved clinically.

Weight Changes.—Section B of Table IV shows that the average gain in weight of 214 SH and S2H patients was 13.4 lb. (6.1 kg.) and that 50% gained 14 lb. (6.4 kg.) or more. The average gain in weight for 168 20 PH and 10 PH patients was 11.6 lb. (5.3 kg.); of these patients 39% gained 14 lb. or more. The difference in average weight gain is significant at the 5% level.

Temperature.—Of 119 pyrexial SH and S2H patients 75% became apyrexial, compared with 80% of 104 20 PH and 10 PH patients (Table V). Of 99 initially apyrexial SH and S2H patients 11% showed a low-grade pyrexia at three months, compared with 9% of 67 20 PH and 10 PH patients.

Sedimentation Rate.—In 145 SH and S2H patients with an initial E.S.R. of 21 or more there was a fall to normal (10 or less) in 38%. For 119 20 PH and 10 PH patients the corresponding figure was 43% (Table VI). In 39 SH and S2H patients with an initially normal E.S.R. there was a rise to 11 or more at three months in 10%, compared with 7% of 27 20 PH and 10 PH patients.

Radiographic Changes in the First Three Months.—The percentages showing radiographic improvement were 77% of 219 SH and S2H patients, and 74% of 172 20 PH and 10 PH patients (Table VII). A higher proportion of the SH and S2H patients showed 2-plus and 3-plus improvement (49%) than of those on 20 PH and 10 PH (38%), the difference between these percentages being significant at the 5% level.

Summary of the Comparison of Streptomycin Plus Isoniazid With P.A.S. Plus Isoniazid

The patients on streptomycin plus isoniazid gained a little more weight and a higher proportion showed substantial radiographic improvement. In other respects the three-month results in the two treatment series are similar.

III. BACTERIOLOGY

This section presents an analysis of the bacteriological findings in those patients whose clinical progress has been reported above. The bacterial content of the sputum is studied after one, two, and three months of treatment. Evidence on the development of bacterial resistance after two and three months of treatment is presented. Resistance to isoniazid is studied for patients under each of the four treatments, to streptomycin for SH and for S2H patients, and to P.A.S. for 20 PH and for 10 PH patients.

The procedure for taking specimens, the technique for sensitivity tests to each of the three drugs, and the definitions of resistance and sensitivity have been described in detail in previous reports (Medical Research Council, 1953a, 1953b). The examinations of bacteriological specimens and the sensitivity tests to isoniazid and to streptomycin were performed in the co-operating laboratories. The P.A.S.-sensitivity tests on cultures from the 20 PH and 10 PH patients were all performed in the reference laboratory (see Acknowledgments).

The result of a bacteriological examination, or of a sensitivity test, for a given month was accepted only if it was performed on a specimen collected not more than seven days before or after the appropriate date. When more than one such result was available, the one referring to a specimen taken on or nearest to the appropriate date was selected to avoid bias. Thus in all the bacteriological tables each item represents a number of *patients* for each of whom a single test has been selected, and not a total of all the *tests* performed on a smaller number of patients.

1. Exclusions

In addition to the patients already excluded from the clinical analysis, a further 5 patients (3 SH, 1 S2H, 1 10 PH) have been excluded from the bacteriological analysis. No tubercle bacilli were seen or isolated from pre-treatment specimens for any of these patients, and although there was no doubt of the diagnosis they did not conform to the bacteriological requirements on entry to the trial. It will be recalled that 6 patients were excluded because they were found to have had bacilli resistant to at least one of the drugs on entry to the trial. The bacteriological as well as the clinical analysis is thus confined to patients whose organisms were sensitive at the start of the trial to both of the drugs they were receiving.

2. Bacterial Content of Sputum

The results at one, two, and three months of the selected single examinations of the sputum for tubercle bacilli are set out in Table VIII. At the end of one month's treatment specimens from 32% of 111 SH patients and 27% of 89 20 PH patients, in Groups 1 and 2 combined, were negative both on direct examination and on culture. At the end of the second month the corresponding figures were 51% of 104 SH patients and 43% of 91 20 PH patients. At three months the figures were 65% of 106 SH patients and 66% of 89 20 PH patients. The figures for the two treatments are very

TABLE VIII.—*Presence of Tubercle Bacilli at Single Examinations Made at Monthly Intervals*

		Months after Entry to Trial	Treatment	Total Patients Examined		"Positive" Direct Examination†		"Scanty Positive" Direct Examination*†		Direct Examination Negative and Culture Positive; or Laryngeal Swab Positive		Direct Examination and Culture Negative; or Laryngeal Swab Negative	
				No	%	No.	%	No.	%	No.	%	No.	%
Section A	Groups 1 and 2 combined	1	SH	111	*99*	36	*32*	6	*5*	33	*30*	36	*32*
			20 PH	89	*100*	26	*29*	9	*10*	30	*34*	24	*27*
		2	SH	104	*100*	21	*20*	4	*4*	26	*25*	53	*51*
			20 PH	91	*100*	22	*24*	6	*7*	24	*26*	39	*43*
		3	SH	106	*100*	10	*9*	4	*4*	23	*22*	69	*65*
			20 PH	89	*99*	11	*12*	1	*1*	18	*20*	59	*66*
	Group 1	3	SH	59	*100*	10	*17*	2	*3*	14	*24*	33	*56*
			20 PH	46	*100*	5	*11*	1	*2*	11	*24*	29	*63*
	Group 2	3	SH	47	*100*	0	*0*	2	*4*	9	*19*	36	*77*
			20 PH	43	*100*	6	*14*	0	*0*	7	*16*	30	*70*
Section B	All patients in Groups 1, 2, and 3 combined	3	SH and S2H	203	*100*	22	*11*	5	*2*	36	*18*	140	*69*
			20 PH and 10 PH	162	*100*	17	*10*	3	*2*	27	*17*	115	*71*

All patients were bacteriologically positive before treatment—that is, at least one pre-treatment specimen showed bacilli on direct examination or was positive on culture.

* Defined as follows: only a few clumps of acid-fast bacilli found after five minutes' search.

† Even if culture-negative.

TABLE IX.—*Results of Isoniazid Sensitivity Tests in SH, S2H, 20 PH, and 10 PH Patients (Excluding Those Found to Have Organisms Resistant to any Drug on Entry to Trial)*

	Months after Entry to Trial	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but Sensitivity Result Not Available	Patients Culture-positive with Sensitivity Tests							Total Resistant		
						Total Results Available (*b*)	Sensitive	Doubtful	Resistant						
							No Growth on 0·2 μg per ml.	Growth on 0·2 μg per ml. Not on 1	Growth on 1 μg per ml. Not on 5	Growth on 5 μg. per ml. Not on 10	Growth on 10 μg. per ml. Not on 50	Growth on 50 μg. per ml.	No (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
Section A (Groups 1 and 2 combined, including subgroup 1A)	2	SH	104	48	3	53	44	8	1	0	0	0	1	*2*	*1*
		20 PH	91	43	3‡	45	39	6	0	0	0	0	0	*0*	*0*
	3	SH	106	67	0	39	36	1	0	1	0	1	2	*5*	*2*
		20 PH	89	59	1	29	25	4	0	0	0	0	0	*0*	*0*
Section B (Groups 1, 2, and 3 combined, excluding subgroup 1A)	2	SH	71	37	2	32	26	6	0	0	0	0	0	*0*	*0*
		S2H	94	49	0	45	36	4	1	2	1	1	5	*11*	*5*
		20 PH	70	38	2	30	24	6	0	0	0	0	0	*0*	*0*
		10 PH	67	37	0	30	29	1	0	0	0	0	0	*0*	*0*
	3	SH	74	56	0	18	16	0	0	2†	0	0	2	*(11)**	*3*
		S2H	94	71	2	21	9	4	4	1	0	3	8	*(38)*	*9*
		20 PH	67	48	1	18	14	4	0	0	0	0	0	*(0)*	*0*
		10 PH	65	49	0	16	13	2	0	0	0	1	1	*(6)*	*2*

* Percentages based upon fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.
† One of these cultures showed growth at 5 μg. per ml., but was not tested at higher concentrations.
‡ See note at foot of page.

similar. It will be noted, however, that at three months the patients with the more acute disease (Group 1) had not fared so well as the Group 2 patients.

Section B of Table VIII presents a supplementary comparison of the effects of streptomycin plus isoniazid and P.A.S. plus isoniazid in all patients. Of 203 SH and S2H patients, specimens from 69% were negative at the end of three months, both on direct examination and on culture, compared with 71% from 162 20 PH and 10 PH patients.

3. Sensitivity Tests

The results of the sensitivity tests at two and three months, on all the SH and 20 PH patients in Groups 1 and 2 combined, appear in Section A of Tables IX–XI.

So far in this report no separate information on the S2H or 10 PH series has been presented, since the numbers of results are at present rather small. These two treatments were included in the trial because they are more readily administered to, and tolerated by, the patient than the SH and 20 PH treatments respectively. However, since a crucial measure of the suitability of these combinations is their ability to prevent the emergence of drug-resistant bacteria, the data on drug resistance, although limited, are sufficiently important to be presented now for each of the four treatments separately. To make valid comparisons between the SH and S2H series, the SH patients in subgroup 1A (who have no counterparts in the S2H series) have been omitted. Similarly, the 20 PH patients in subgroup 1A have been omitted from the comparison between the 20 PH and 10 PH series. The small numbers of Group 3 patients have been retained in the analysis. The results of these comparisons appear in Section B of Tables IX–XI.

Isoniazid Sensitivity.—The results of the isoniazid-sensitivity tests are set out in Table IX. At three months results were available for 39 positive cultures from 106 SH patients; 2 of the cultures yielded resistant strains. The corresponding figures for 89 20 PH patients were 29 positive cultures, none of which yielded resistant strains. The incidence of isoniazid resistance for a period of three months is thus low with each treatment.‡

Turning to the comparison between the SH and S2H treatments, and between the 20 PH and 10 PH treatments (Section B of Table IX), it will be seen that at three months cultures were found to be resistant from 2 of 18 patients on SH compared with 8 of 21 on S2H and from 0 of 18 on 20 PH compared with 1 of 16 on 10 PH. The least satisfactory figures are those for the S2H treatment, for which the resistant cultures at three months represent 38% of all positive cultures, compared with 11% for the SH series; they represent 9% of all the patients for whom cultures were undertaken, compared with 3% for the SH series. At two months also the results for the S2H series are inferior to those for the SH series, 5 of 45 positive cultures from S2H patients being resistant to isoniazid, compared with 0 of 32 cultures from SH patients. The findings in the 10 PH series at two and three months, on the other hand, are almost as satisfactory as in the 20 PH series, although the numbers are small.

Streptomycin Sensitivity.—At two months 1 of 52 cultures from 104 SH patients was resistant to streptomycin (Table X). At three months there was one resistant strain among 38 cultures from 106 patients. The SH combination is thus effective for at least three months in preventing the emergence of bacilli resistant to streptomycin.

The comparison of the SH and S2H treatments in Section B of Table X shows that 0 of 18 cultures from 74 SH patients, and 3 of 22 cultures from 94 S2H patients, were streptomycin-resistant at the end of three months.

P.A.S. Sensitivity.—At two months 2 of 47 cultures from 91 20 PH patients were resistant to P.A.S. (Table XI). At three months there was 1 resistant strain among 28 cultures from 89 patients. The 20 PH combination is thus effective for a three-month period in preventing the emergence of bacilli resistant to P.A.S.

The comparison of the 20 PH and 10 PH treatments in Section B of Table XI shows that 1 of 18 cultures from 67 20 PH patients, and 1 of 14 from 65 10 PH patients, were P.A.S.-resistant at the end of three months.

‡Special reference must be made to the results of isoniazid-sensitivity tests at two months in 3 20 PH patients. All were from one small centre which had recently entered the trial, and they represent the total contribution of the centre to the two treatment series receiving P.A.S. plus isoniazid.

The cultures from two of these patients were reported at the local laboratory as resistant at two months to isoniazid, and were submitted as usual to the reference laboratory for confirmation of the level of resistance. In the reference laboratory, however, both cultures were found to be sensitive to isoniazid. The two cultures were subsequently retested both locally and centrally and the results in both laboratories were sensitive. The culture from the third patient was accidentally discarded at the local laboratory and a test at the reference laboratory gave a sensitive result. However, a culture at six weeks on the same patient had been reported as resistant to isoniazid at the local laboratory, but sensitive at the reference laboratory. At three months specimens from all 3 patients were negative on culture, so that no sensitivity tests were possible.

It must be realized that the check-tests were made on cultures which had been kept for some while before testing, and in one instance on a subculture; any isoniazid resistance may have diminished in the interval. On the other hand no isoniazid-resistant strains, either in 20 PH or in 10 PH patients, were reported at two months from any other centre. In these circumstances it was decided with the local bacteriologist that the results of these tests should be regarded as equivocal. They have been entered as "Culture-positive, sensitivity test not available."

TABLE X.—*Results of Streptomycin Sensitivity Tests in SH and S2H Patients (Excluding Those Found to have Organisms Resistant to any Drug on Entry to Trial)*

	Months after Entry to Trial	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but Sensitivity Result not Available	Patients Culture-positive with Sensitivity Tests				Total Resistant		
						Total Results Available (*b*)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	No. (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
Section A (Groups 1 and 2 combined, including subgroup 1A)	2	SH	104	48	4	52	51	1	0	1	*2*	*1*
	3	SH	106	67	1	38	37	1	0	1	*3*	*1*
Section B (Groups 1, 2, and 3 combined, excluding subgroup 1A)	2	SH	71	37	2	32	31	1	0	1	*3*	*1*
		S2H	94	49	1	44	42	2	0	2	*5*	*2*
	3	SH	74	56	0	18	18	0	0	0	*(0)**	*0*
		S2H	94	71	1	22	19	2	1	3	*(14)*	*3*

* Percentages based upon fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

TABLE XI.—*Results of P.A.S. Sensitivity Tests in 20 PH and 10 PH Patients (Excluding Those Found to have Organisms Resistant to any Drug on Entry to Trial)*

	Months after Entry to Trial	Treatment	Total Patients with Culture Examined (*a*)	Culture-negative (No Sensitivity Test Possible)	Culture-positive but Sensitivity Result not Available	Patients Culture-positive with Sensitivity Tests				Total Resistant		
						Total Results Available (*b*)	Sensitive	Moderately Resistant (Ratio 8 to 99)	Strongly Resistant (Ratio 100 or More)	No. (*c*)	(*c*) as % of (*b*)	(*c*) as % of (*a*)
Section A (Groups 1 and 2 combined, including subgroup 1A)	2	20 PH	91	43	1	47	45	2	0	2	*4*	*2*
	3	20 PH	89	59	2	28	27	0	1	1	*4*	*1*
Section B (Groups 1, 2, and 3 combined, excluding subgroup 1A)	2	20 PH	70	38	0	32	30	2	0	2	*6*	*3*
		10 PH	67	37	3	27	27	0	0	0	*0*	*0*
	3	20 PH	67	48	1	18	17	0	1	1	*(6)**	*1*
		10 PH	65	49	2	14	13	1	0	1	*(7)*	*2*

* Percentages based upon fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

IV. DISCUSSION

In the first report of this trial (Medical Research Council, 1952) it was shown that isoniazid was an effective drug in the treatment of pulmonary tuberculosis, but that when it was used alone resistant bacteria emerged frequently and rapidly. This finding indicated the importance of combining isoniazid with other drugs active against tuberculosis, in order to find a treatment which was bacteriologically as well as clinically effective.

Accordingly, from September 5, 1952, four combined treatments have been investigated—namely, streptomycin 1 g. daily plus isoniazid (SH), streptomycin 1 g. twice a week plus isoniazid (S2H), P.A.S. (sodium salt) 20 g. daily plus isoniazid (20 PH), and P.A.S. (sodium salt) 10 g. daily plus isoniazid (10 PH). The dosage of isoniazid was 200 mg. daily in each treatment. Over 600 patients have now been given one of these four treatments, allocated concurrently and at random, and this report presents clinical and bacteriological results at three months on 391 of these patients who were admitted to the trial before March 31, 1953. For reasons given, the main comparison in the report is between the SH and 20 PH treatments, the results at the end of three months being summarized in Table XII. Over this limited period the two treatments were of comparable efficacy in improving the general clinical condition, in lowering the sedimentation rate, in resolving pyrexia, and in suppressing tubercle bacilli in the sputum. Patients on the SH treatment gained more weight and a rather higher proportion showed substantial radiographic improvement, but on present totals the differences are not statistically significant.

In the second report of the trial (Medical Research Council, 1953a) it was concluded that streptomycin 1 g. daily plus isoniazid 200 mg. daily was clinically the most effective anti-tuberculosis chemotherapy yet investigated in the trial, although its superiority to streptomycin 1 g. daily plus P.A.S. (sodium) 20 g. daily was not great. The new information now presented on the clinical efficacy of P.A.S. (sodium) 20 g. daily plus isoniazid indicates that this combination is a powerful addition to the acceptable drug treatments of pulmonary tuberculosis over a three-month period. Further evidence of the

TABLE XII.—*Summary of Comparisons of Streptomycin 1 g. Daily Plus Isoniazid 200 mg. Daily With P.A.S. (Sodium) 20 g. Daily Plus Isoniazid 200 mg. Daily at the End of Three Months' Treatment*

	Streptomycin 1 g. Daily plus Isoniazid (%)	P.A.S. (Sodium) 20 g. Daily plus Isoniazid (%)
General condition:		
Improvement 2-plus	*34*	*38*
,, 1-plus	*54*	*51*
No change	*10*	*11*
Deterioration	*0*	*0*
Death	*1*	*1*
Weight:		
Gain 14 lb. (6·4 kg.) or more	*45*	*38*
,, 7–13 lb. (3·2–6·3 kg.)	*31*	*29*
,, less than 7 lb., or no change	*20*	*26*
Loss	*4*	*8*
Temperature:		
Afebrile at 3 months (febrile at start)	*79*	*85*
Erythrocyte sedimentation rate:		
Fall to normal from 21 or more in 3 months	*37*	*46*
Radiograph:		
Improvement 2-plus or 3-plus	*54*	*42*
,, 1-plus	*28*	*34*
No change	*16*	*20*
Deterioration	*2*	*2*
Sputum:		
At 3 months: Direct positive	*13*	*13*
Positive culture only	*22*	*20*
Negative	*65*	*66*
Isoniazid sensitivity (positive cultures):		
At 3 months: Sensitive	*92*	*86*
Doubtful	*3*	*14*
Resistant	*5*	*0*

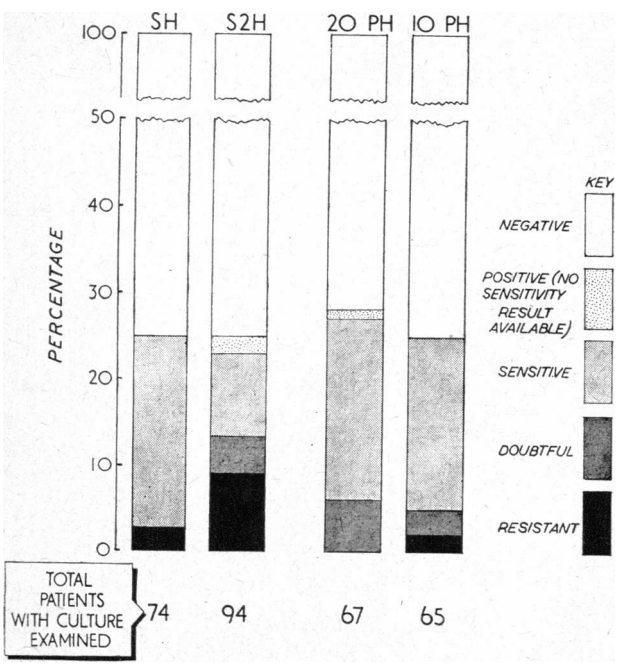
See Tables III–IX for the numbers of patients on which these percentages are based. See Tables X and XI for the results of the streptomycin- and P.A.S.-sensitivity tests.

efficacy of combining P.A.S. with isoniazid is provided by the supplementary analysis of the progress of the 20 PH and 10 PH patients combined, which presents results for a much larger number of patients.

It was also shown in the second report that the combination streptomycin 1 g. daily plus isoniazid effectively hindered the emergence of bacilli resistant either to isoniazid or to streptomycin; the present report confirms these findings on a further series of patients, who were on the whole suffering from more acute forms of the disease. At three months 39 cultures from 106 patients were isolated and tested for isoniazid sensitivity, and 2 were resistant; 1 of 38 cultures from the same number of patients was resistant to streptomycin. The combination P.A.S. (sodium) 20 g. daily plus isoniazid is no less effective in preventing the emergence of strains resistant either to isoniazid or to P.A.S. At three months 29 cultures from 89 patients were tested for isoniazid sensitivity, and all were sensitive; 1 of 28 cultures from the same number of patients was resistant to P.A.S. For a three-month period the 20 PH treatment is thus bacteriologically as well as clinically effective. As an indication of the ability of the 20 PH combination to prevent the emergence of isoniazid-resistant strains, it will be recalled that in an earlier stage of the trial 64% of 132 positive cultures from 243 patients on isoniazid alone were resistant at three months (Medical Research Council, 1953c).

Before a valid comparison of the relative efficacy of the four treatments SH, S2H, 20 PH, and 10 PH could be made, it was necessary to exclude the patients in subgroup 1A, who were allocated only to the SH and 20 PH treatments. When this was done, no marked differences in clinical response were apparent between patients on each of the four treatments, but a full clinical evaluation must await the results for the larger number of patients now under study. However, the bacteriological information already available, although based upon small numbers, is of sufficient importance to warrant discussion.

The results of sensitivity tests for the 20 PH and the 10 PH patients at three months showed practically no development of bacterial resistance, either to isoniazid (see Chart) or to P.A.S., in patients on either of these treatments. The finding that 10 PH appears to be bacteriologically an effective treatment should lend particular interest to the detailed study, in due course, of the clinical findings in 10 PH patients.



Results of isoniazid-sensitivity tests at three months.

The preliminary comparison of the results of sensitivity tests for the SH and S2H patients at three months indicates a less satisfactory situation for the latter treatment. Although the development of streptomycin resistance was largely prevented by each combination, the incidence of isoniazid-resistant strains at three months (see Chart) was noticeably greater for the S2H than for the SH patients. If, on larger numbers, this difference is confirmed, it will represent a definite disadvantage of the combination streptomycin 1 g. twice a week plus isoniazid.

In conclusion, this analysis has demonstrated that P.A.S. (sodium) 20 g. daily plus isoniazid 200 mg. daily, when used for a three-month period, is very effective, both clinically and bacteriologically, in the treatment of pulmonary tuberculosis. It ranks with the most efficacious chemotherapeutic combinations so far tested in this trial—namely, streptomycin 1 g. daily plus isoniazid 200 mg. daily and streptomycin 1 g. daily plus P.A.S. (sodium) 20 g. daily. It possesses an advantage over these two established treatments in that both drugs are administered by mouth.

V. SUMMARY

As part of a clinical trial of isoniazid (isonicotinic acid hydrazide) in the treatment of pulmonary tuberculosis, 391 patients were studied in 50 hospitals: 119 were treated with streptomycin (1 g. daily) plus isoniazid (100 mg. twice a day), 100 with streptomycin (1 g. twice a week) plus isoniazid (100 mg. twice a day), 101 with P.A.S. (sodium salt, 5 g. four times a day) plus isoniazid (100 mg. twice a day), and 71 with P.A.S. (sodium salt, 5 g. twice a day) plus isoniazid (100 mg. twice a day). When submitting a case the physician did not know which treatment the patient would receive, this being determined by random allocation. The present report analyses results at the end of three months' treatment.

Three main groups were observed: Group 1, acute rapidly progressive disease of recent origin; Group 2, other forms considered suitable for chemotherapy; Group 3, chronic disease considered unlikely to respond to chemotherapy.

For reasons given, the principal comparison in the report is between the patients in Groups 1 and 2 on streptomycin 1 g. daily plus isoniazid 200 mg. daily (SH) and those on P.A.S. (sodium) 20 g. daily plus isoniazid 200 mg. daily (20 PH). (A full comparison of all four treatments will be made when results for more patients are available.)

On admission, these two treatment series had a similar distribution of patients with severe and less severe illness. At the end of three months the general condition had improved in 89% of the SH patients and 88% of the 20 PH patients. The average gain in weight during the period was 12.8 lb. (5.8 kg.) for the SH patients and 10.8 lb. (4.9 kg.) for the 20 PH patients. The temperature fell to normal in 79% of febrile SH patients and 85% of febrile 20 PH patients. In patients with an E.S.R. of 21 or more before treatment the rate fell to 10 or less in 37% of those on SH, compared with

46% of those on 20 PH. Changes in radiographic appearances were independently assessed by a radiologist unaware of the treatment of any patient. Two-plus or three-plus improvement was seen in 54% of SH and 42% of 20 PH patients. There were two radiographic deteriorations and one death on each treatment. None of the above differences is statistically significant.

The proportion of patients bacteriologically negative, both on direct examination and on culture, at a single examination at three months was 65% for the SH series and 66% for the 20 PH series.

Bacillary resistance to isoniazid was found in 2 of 39 culture-positive SH patients tested at three months, compared with 0 of 29 similar 20 PH patients. Bacillary resistance to streptomycin was found in 1 of 38 culture-positive SH patients, and to P.A.S. in 1 of 28 similar 20 PH patients.

It is concluded, *judging solely from the results at three months,* that P.A.S. (sodium) 20 g. daily plus isoniazid 200 mg. daily is a very effective combination of drugs, both clinically and bacteriologically; it ranks with the most efficacious treatments so far studied—namely, streptomycin 1 g. daily plus isoniazid 200 mg. daily and streptomycin 1 g. daily plus P.A.S. (sodium) 20 g. daily.

A supplementary clinical comparison of all the 219 patients on streptomycin plus isoniazid and all the 172 on P.A.S. plus isoniazid confirms the clinical efficacy of combining P.A.S. with isoniazid. However, patients on streptomycin plus isoniazid gained a little more weight, and a higher proportion showed substantial radiographic improvement.

A preliminary analysis of results of sensitivity tests on each of the four treatments shows that P.A.S. (sodium) 10 g. daily plus isoniazid 200 mg. daily may prove to be a bacteriologically effective combination for at least three months. On the other hand, treatment with streptomycin 1 g. twice a week plus isoniazid 200 mg. daily is apparently less effective than streptomycin 1 g. daily plus isoniazid 200 mg. daily in preventing the development of bacterial resistance to isoniazid over a three-month period.

ACKNOWLEDGMENTS

The hospitals and the doctors co-operating in the phase of the trial reported here are as follows:

Hospitals.—Aberdeen City Hospital; Aintree Hospital; Ashludie Hospital, Monifieth; Ayrshire Central Hospital, Irvine; Bangour Hospital, West Lothian; Black Notley Hospital, Braintree; Brierton Hospital, West Hartlepool; British Legion Sanatorium, Nayland; Brompton Hospital; Broomfield Hospital, Chelmsford; Canadian Red Cross Memorial Hospital, Taplow; Clare Hall Hospital, Herts; Connaught Military Hospital; Cumberland Hospital, Surrey; Dumfries and Galloway Sanatorium; East Fortune Hospital, East Lothian; Edgware General Hospital; Edinburgh City Hospital; Foxhall Hospital, Ipswich; Glenafton Hospital, Ayrshire; Hammersmith Hospital; Heathcote Hospital, Leamington Spa; Heathfield Hospital, Ayrshire; Hillingdon Hospital; Holywood Hall Sanatorium, Bishop Auckland; Inverurie Hospital, Aberdeen; Kettlewell Hospital, Kent; King Edward VII Sanatorium, Midhurst; King George V Hospital, Godalming; King George's Sanatorium for Sailors, Hants; Lenham Sanatorium, Kent; Llangwyfan Hospital, Denbigh; Mearnskirk Hospital, Renfrewshire; Mount Pleasant Hospital, Middlesex; Newcastle General Hospital; North Middlesex Hospital; Poole Sanatorium, Middlesbrough; Robroyston Hospital, Glasgow; Romsley Hill Sanatorium, Worcestershire; Royal Victoria Hospital, Edinburgh; St. Albans City Hospital; St. Helen's Hospital, Ipswich; St. Helier Hospital, Surrey; Seaham Hall Sanatorium, Sunderland; Southfield Hospital, Edinburgh; Westcliffe Hospital; West Heath Sanatorium, Birmingham; Woodend Hospital, Aberdeen; Wooley Sanatorium, Northumberland; Yardley Green Hospital, Birmingham.

Physicians.—Drs. P. G. Arblaster, M. Barry, D. Bell, W. Biagi, W. M. Borthwick, J. T. Boyd, L. E. Burkeman, K. M. Chalmers, J. A. Chamberlin, C. W. Clayson, R. C. Cohen, A. H. C. Couch, Professor J. W. Crofton, Drs. R. Cunningham, V. Davies, V. F. Dawkins, M. K. Dhole, J. W. Duerden, T. A. Watkin Edwards, I. Elmslie, W. J. Ferraby, P. Forgacs, M. A. Foulis, R. Fraser, M. A. Gallagher, J. E. Geddes, I. W. B. Grant, J. S. B. Greenfield, L. A. Hardie, W. C. Harris, H. F. Harwood, M. Hemming, E. V. Hess, J. A. Hill, F. Hodgkiss, N. W. Horne, J. V. Hurford, G. Hurrell, J. E. M. Hutchinson, Lieutenant G. J. Jones, Drs. G. Penrhyn Jones, R. Sinclair Kennedy, G. M. Lewis, G. M. Little, L. C. Lum, E. G. Sita Lumsden, G. R. W. N. Luntz, Lieutenant-Colonel J. Mackay-Dick, Drs. W. MacDermid, N. MacFarlane, D. G. McIntosh, G. R. McNab, A. T. Mason, W. T. Miller, K. Murray, W. A. Murray, P. J. O'Rooney, J. P. Parkinson, Hayden J. Partington, W. C. Pinkney, A. C. P. Ritchie, J. B. Robinson, J. T. Nicol Roe, Hector J. T. Ross, I. D. Ross, J. D. Ross, J. B. M. Runciman, F. A. H. Simmonds, D. H. Smith, J. Morrison Smith, J. Stevenson, C. J. Stewart, P. Stradling, G. J. Summers, J. Sumner, J. O. Taubman, D. Teare, H. E. Thomas, O. F. Thomas, B. C. Thompson, H. R. Thomson, Sir Geoffrey S. Todd, Drs. H. J. Trenchard, F. W. A. Turnbull, M. Walton, W. F. Wheeler, A. B. White, F. L. Wollaston, W. L. Yell, D. van Zwanenberg, and the consultant staff of Brompton Hospital (registrar, R. N. Johnston).

Bacteriologists and Pathologists.—Drs. C. S. Anderson, D. F. Barrowcliff, R. Blowers, D. M. H. Cogman, R. T. Cooke, J. E. Craik, P. B. Crone, J. C. Dick, Professor A. W. Downie, Drs. J. M. Dunbar, W. J. Godden, T. E. W. Goodier, W. I. Gordon, J. Harper, J. F. Heggie, E. D. Hoare, Captain C. H. Jones, Drs. E. R. Jones, P. Kidd, M. Laidlaw, G. Laws, J. T. A. Lloyd, A. Macdonald, J. Marks, P. H. Martin, A. Messer, D. A. Mitchison, Squadron-Leader A. D. Moore, Drs. E. Nassau, J. W. Nicholas, W. H. A. Picton, R. Pilsworth, Squadron-Leader J. S. Porterfield, Drs. A. I. D. Prentice, I. A. Purdie, K. Rafinski, R. W. Riddell, J. M. Robertson, B. R. Sandiford, F. E. T. Scott, A. G. Signy, T. Skeoch, J. Smith, P. J. Taylor, W. K. Taylor, A. T. Wallace, R. F. Welch, W. Whitelaw. The bacteriologists and pathologists form a laboratory subcommittee under the chairmanship of Professor R. Cruickshank.

Dr. E. H. Bailey, Southern Group Laboratory, supplied culture medium where desired. Dr. D. A. Mitchison's laboratory, Postgraduate Medical School of London, served as reference laboratory for drug-resistance tests.

The above cannot be a comprehensive list of all the doctors who have contributed to the results reported here, nor has it been possible to name the many laboratory technicians who have done detailed and valuable work. The Tuberculosis Chemotherapy Trials Committee expresses its thanks to all members of hospital staffs who have assisted in the investigation, particularly for their willing response to the urgent requests for information for inclusion in this report.

The Research Committee of the Tuberculosis Society of Scotland was of considerable assistance in initiating the trial in Scotland. The Edinburgh team is in receipt of a research grant from the Royal Victoria Hospital Tuberculosis Trust. The figure was drawn by Miss P. Carter, of the Department of Medical Illustration, Guy's Hospital.

REFERENCES

Medical Research Council (1952). *British Medical Journal*, **2**, 735.
—— (1953a). Ibid., **1**, 521.
—— (1953b). *Lancet*, **2**, 213.
—— (1953c). Ibid., **2**, 217.

DESENSITIZATION TO STREPTOMYCIN AND P.A.S.

BY

JOHN CROFTON, M.D., F.R.C.P.

From the Department of Tuberculosis and Diseases of the Respiratory System, University of Edinburgh

It is not proposed to discuss in detail in this paper the symptoms of hypersensitivity to streptomycin or P.A.S. (para-aminosalicylic acid), but only to emphasize that desensitization is possible. In patients sensitized by treatment with streptomycin or P.A.S. desensitization is usually easy, and has been referred to briefly elsewhere (Crofton, 1953). It is much more difficult to desensitize individuals sensitized to streptomycin by handling it in the course of their work, and I have seen no previous report of this being successfully accomplished.

Desensitization of Streptomycin-handlers

The recent statement from the Ministry of Health (1953) indicates that a number of people whose duty involves the handling of streptomycin become sensitized to the drug. In many cases the degree of sensitivity is very high; a nurse may not only be unable to administer streptomycin injections but may be unable to work in a ward where they are given or enter a room where the injections are prepared. The previous literature on this subject has been well reviewed in the Ministry of Health report and will not be recapitulated here. The present report is only to emphasize that even individuals highly sensitive to streptomycin can be desensitized, and to describe two cases in which this has been done.

Case 1

A ward sister aged 37 had no family or personal history of allergy. Two years before admission to hospital she had begun giving streptomycin injections, and during the five